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EXAMINER	
RICIGLIANO,J	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/884,873	Applicant(s) Cook, Philip Dan
	Examiner Joseph W. Ricigliano Ph. D.	Group Art Unit 1627

☒ Responsive to communication(s) filed on *Feb 7, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *2-19, 24-30, and 32* is/are pending in the application.

Of the above, claim(s) *27-30* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *2-19, 24-26, and 32* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

1. This action is responsive to the election of species filed 02/07/2000.

Status of the claims

2. Claims 2-19, 24-30 and 32 are pending in the instant application. Claims 27-30 stand withdrawn from consideration as being drawn to a nonelected invention. Claims 2-19, 24-26 and 32, drawn to the invention of group I are being examined on their merits

Response to Remarks

3. Applicant's representative remarks that the examiner agreed during the interviews conducted on September 7 and 8 that applicant would amend the claims to insert the structures now recited in claim 32 as I, II and III. With respect to this remark the examiner notes the potential for these amendments to introduce new matter was also discussed with applicant's representative.

Specification

4. The disclosure is objected to because of the following informalities:

The structures set forth on pages 35 and 38 in the first lines have purines to which are attached nitrogens that do not have their valencies filled (e.g., they are missing two hydrogens to make them amines, etc.).

Appropriate correction is required.

Claim Objections

5. Claims 14-16 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

6. Claims 14 and 15 recite the limitation that the compound of the claimed mixtures are synthesized simultaneously in solution, or simultaneously in solution through an "interative" process. These are process limitation which fails to further limit mixtures claimed.

7. Claim 15 recites interative instead of "iterative."

8. Claim 16 recites the limitation that at least one of the functionalizable atoms of the compounds is blocked and subsequently deblocked. This is a process limitation which fails to further limit mixtures claimed.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 32 and its dependent claims 2-19 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As amended independent claim 32 and its dependent claims 2-19 and 24-26 appear to introduce new matter in several ways:

With respect to the claim as a whole:

The amended claims now recite "[A] mixture comprising at least six chemical compounds having one of structures I, II and III..." This recitation permits the formation of mixtures which have more than one of the core structures I, II or III present, (e.g., both purines and pyrimidines simultaneously in the same mixture etc.). There appears to be no support in the original disclosure for such mixtures. Moreover, the instant recitation contrasts markedly with the original claim language which recited "[A] mixture of chemical compound each having a common purine or pyrimidine heterocyclic scaffold..." in which the mixtures require a common scaffold to be present for all six required compounds.

With respect to the tethers:

The tether "T" formula as set forth in claim 32 does not appear to be supported in the specification.

With respect structure I and mixtures comprising said structure:

The original disclosure does not appear to support the specific formation of mixtures of structure I (in the presence or absence of structures II or III as discussed above). There appears to be no support in the original disclosure for the use of the specific sites on the pyrimidine nucleus in combination with the tether moieties and the specific L moieties as now claimed.

With respect structures II and III and mixtures comprising said structure:

The original disclosure does not appear to support the specific formation of mixtures of structures II or III (alone, in admixture with each other or in admixture with structure I). There appears to be no support in the original disclosure for the use of the specific combination of sites on the purine nuclei in combination with the tether moieties and the specific L moieties as now claimed. Moreover, there does not appear to be support for either the introduction of subscripts e and j in the structures or the proviso that the sum of e and j is 1.

For at least these reasons the claims appear to introduce new matter.

11. *Applicant's arguments filed 10/6/99 have been fully considered but they are not persuasive. Claim 31 has been canceled and the instant claims have been amended to depend directly or indirectly from claim 32. The structures and mixtures of compounds set forth in the instant claims (some of which were previously recited in claim 31 and its dependent claims) do not appear to be supported by the original disclosure contrary to applicants arguments.*

Applicants argue that the formula for the tether group is supported on: page 3 line 27-page 4 line 3, page 5, line 25-page 6, line 2 and page 16 lines 17-34. This argument has been considered but is not found persuasive because passages do not support the specific structures set forth in the claims.

Applicants argue that the specific examples support the purine and pyrimidines compounds set forth in the claims. These arguments have been considered but are not found persuasive because the specific examples do not support the full scope of the claimed combinations tethers and linkers being used to modify the specific scaffold positions now

claimed or the scope of the mixtures of compounds which would result from combining such compounds.

12. Claims 17 and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 17 and 18 have been amended to recite that at least some of the chemical compounds in the mixture are subsequently further substituted with a chemical substitutent. As amended the claims encompass adding substituent onto substituent (i.e., letters onto letters) or more than one substituent (letter) onto a tether. The specification does not appear to support mixtures formed in this manner. This rejection can be overcome by indicating where support can be found in the original disclosure for the claimed subject matter.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 2-19, 24-26 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. Claims 2-19, 24-26 and 32 recite that L can be: a conjugate group, a drug, a metal coordination group. a nucleosidic base and an amino acid side chain . Each of these terms is

vague and indefinite because it is not possible to determine the metes and bounds of the structures or resulting compounds encompassed by these claim limitations. As such, it is not possible to clearly and distinctly determine which mixtures are encompassed by the invention as claimed.

16. Claims 2-19, 24-26 and 32 recite mixtures of six compounds "having one of structures I, II and III" this is vague and indefinite as it is unclear what comprises the required mixtures. As written the claim can be interpreted as compounds of structure I (pyrimidine), and structure II and III (i.e., purine) or the claim can be read as "one of structures I, II **or** III." Atlerntively the claim can be read as encompassing mixtures wherein both purine and pyrimidines are present. In view of the foregoing, it is not possible to determine the metes and bounds of the invention as claimed. If applicant intends this to be a Markush reciting mixtures of six purines of structure III or mixtures of six purines of structure II or mixtures of six pyrimidines of structure I then applicant may wish to use standard Markush type language. In order to proceed with more compact prosecution the examiner has read the claim as being directed to mixtures comprising at least six purines of structure III or mixtures of at least six purines of structure II or mixtures of at least six pyrimidines of structure I.

17. Claims 7 and 9 recite mixtures wherein at least one of the functional atoms on the heterocyclic scaffold is nucleophilic. This is vague and indefinite as it is unclear what structures are encompassed by this limitation as the conditions under which the scaffold structures are to be evaluated for the presence of nucleophiles are not set forth. As such, it is not possible to determine the metes and bound of the invention as claimed.

Applicant's arguments filed 10/6/99 have been fully considered but they are not persuasive. Applicant argues that nucleophilic refers to electron-rich and not the conditions under which the scaffolds might react. The argument is not found persuasive because the claim does not permit one to determine what structures are encompassed and therefore what mixtures are included or excluded from the metes and bounds of the claims.

18. Claim 10 recites the limitation "the tether moiety is substituted with a set of chemical substituents." This is vague and indefinite because it does not clearly and distinctly set forth the metes of the substituted tether moieties encompassed by the claim. Therefore, is not possible to determine the metes and bounds of the claimed subject matter.

19. Claim 13 recites the limitation that at least one functionalizable atom of the heterocyclic scaffold is blocked. This is vague and indefinite as it is unclear if applicants intend this to mean that the sites are already modified with a substituent or if the sites are protected by a protective group. As such, it is not possible to determine the metes and bounds of the claimed subject matter.

20. Claims 11 and 12 recite mixtures wherein in at least one of the functional atoms on the heterocyclic scaffold is electrophilicphilic. This is vague and indefinite as it is unclear what structures are encompassed by this limitation as the conditions under which the scaffold structures are to be evaluated for the presence of electrophiles are not set forth. As such it is not possible to determine the metes and bound of the invention as claimed.

Applicant's arguments filed 10/6/99 have been fully considered but they are not persuasive. Applicants argue that electrophilic refers to electron-deficient and not the

conditions under which the scaffolds might react. The argument is not found persuasive because the claim does not permit one to determine what structures are encompassed and therefore what mixtures are included or excluded from the metes and bounds of the claims.

21. Claims 17 and 18 recite that at least some of the chemical compounds in the mixture are subsequently further substituted with a chemical substitutent. This is vague and indefinite as it is unclear what substituent are being applied to the compounds and to what they are being attached (note that especially in claim 18 the heterocyclic portion has no antecedent basis and could refer to the scaffold or the heterocyclic letters which might be present). Therefore, it is not possible to clearly and distinctly determine the structures of the compounds present in the mixtures and hence the metes and bound of the invention as claimed.

Applicant's arguments filed 10/6/99 have been fully considered but they are not persuasive.

Applicant argues that the specification on pages 12-14 describes the substituent encompassed by the invention. This argument is not found persuasive because applicant is arguing limitations of the specification not found in the claims. Moreover, the claims are not limited to the modification of the scaffolds by attaching a substituent. As recited, the claims encompass attaching substituent onto any portion of the compounds present in the mixture including a previously attached substituent (i.e., a letter being attached to a letter, in applicants terms).

22. Claim 18 recites the limitation "the heterocyclic portion" this is vague and indefinite as it is unclear if it refers to the scaffold portion of the compounds, or if it refers to substituents of the

moieties attached to the scaffold, i.e., "letters." Therefore, it is not possible to determine the metes and bound of the subject matter as claimed.

23. Claim 19 recites "wherein the heterocyclic portion of said chemical compounds are ring-opened, ring expanded, bicyclized, or altered in subsequent to said substitution at said at least one of said funtionalizable atoms." This is indefinite because upon ring-opening, ring expansion, bicyclization, or alteration subsequent to the substitution at one funtionalizable atoms by unstated processes with unspecified reagents it is not be possible to clearly define the structure of the products. Therefore it is not possible to clearly define the metes and bounds of the claimed invention.

24. Applicant's arguments filed 10/6/99 have been fully considered but they are not persuasive. Applicant argues that the substituents are set forth on page 12 line 1 - age 14 line 30 and therefore the skilled artisan would know would have a choice of chemical substituent that may be used in art recognized reactions. This argument is not found persuasive because applicants are arguing limitations of the specification not found in the claims with respect to the substituents. Moreover, the argument do not address the fundamental point of the rejection, which is that it is not possible to clearly and distinctly determine the metes and bound of the claimed subject matter when the claim fails to distinctly set forth substituents being employed, and the reactions used to alter the heterocycles.

25. Claim 19 recites the phase "ring closed" in relation to the purine or pyrimidine heterocyclic scaffolds. Since these scaffolds are already ring structures, the concept of closing a ring in the heterocycle portion of these structures is vague and indefinite. For example it is unclear

if applicant intends to close a new ring bridging a pyrimidine or purine scaffold or if applicant intends to close the substituents attached to a pyrimidine to form a purine or other heterocyclic structure, etc. Therefore, it is not possible to clearly define the metes and bound of the claimed invention.

26. Claim 18 recites the limitation "the heterocyclic portion" in line 2. There is insufficient antecedent basis for this limitation in the claim.

27. Claim 11 recites the limitation "the set of chemical substituents" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

28. Claim 12 recites the limitation "said chemical substitutents" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

29. Claim 13 recites the limitation "the set of chemical substituents" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 101

In view of applicants amendments to remove the structure bearing a pentavalent carbon the rejection under 35 USC 101 and the related rejection under 112 first paragraph are withdrawn.

Claim Rejections - 35 USC § 102

30. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

31. Claims 2-3, 5-15, and 17-19 and 32 are rejected under 35 U.S.C. 102(b) as anticipated or in the alternative under 35 USC 103(a) as being unpatentable over Pavia et al WO95/044277 considering the teaching of Gordon et al [J. Med. Chem. (1994)].

Pavia et al teach a structurally diverse universal library. Pavia et al teach that their libraries are composed of scaffold molecules and at least three functional groups (page 4 line 26) which reads on a scaffold having at least three functionalizable atoms and being substituted at two or more positions. Pavia et al teach that "more preferred" scaffold groups include a pyrimidine rings (page 7 line 21-23) which reads on one of the heterocyclic scaffolds recited in claim 32 in the alternative. Pavia et al teach that the libraries of their invention can be prepared on a solid phase or in solution, (pages 16-17) where in the reactions are conducted simultaneously in a limited number of individual reaction vessels, which reads on reacting multiple compounds together in a mixture. The libraries prepared by Pavia et al can be synthesized by combinatorial methods and contain more than one million compounds, which reads on libraries containing least 6, 10 or 15 compounds (page 16). Pavia et al also teach the use of more than six chemical substituents to substitute the scaffold (see R and W groups on page 6) and the tether groups connecting the chemical substituents to the scaffold (see the A, M or M-bound to a second ring on page 6) which reads on at least six different chemical substituents and the tether groups of the instant invention. On pages 5-7 Pavia et al each that their tethers and scaffolds include nitrogen substituted nitrogen (NR_{60}, which reads on a functionalizable tether atom which is nucleophilic,

substituted and on the scaffold; see the limitations of claims 7-10); S (which reads on a nucleophile) and alkenes (which reads on an electrophile). Pavia et al teach other substituents that can be electrophilic or nucleophilic on their scaffolds; for example a Br-substituted alkane has an electrophilic carbon and the -SH moiety reads on a nucleophile. As noted above, Pavia et al teach adding substituents to functionalizable atoms (for example the addition of a W group, see pages 5-7), which reads on blocking the functionalizable atoms, a specific limitation of claim 13. Pavia also teaches deprotecting mixtures (see scheme Va, page 36 for example), which reads on reacting mixtures with a further reactant. Pavia teaches the addition of a second (and a third) set of substituents to an already formed mixture which reads on reacting a mixture with a further reactant at the heterocyclic portion and altering subsequent to substitution, limitations of claims 18 and 19 (see scheme I-III page 21 and pages 5-7).

In the alternative one could argue that the passages in Pavia et al on pages 16-17 do not explicitly state that one forms mixtures of the pyrimidine compounds.

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to form mixtures of pyrimidines when preparing libraries as taught by Pavia et al because forming mixtures to conduct the common chemical reactions for library members was well-known in the art at the time the invention was made. This is clearly evidenced by the teachings of Gallop et al which establish that split and combine synthesis techniques were well established in the art at the time of the invention (see for example figure 7 on page 1390 and related text). One of ordinary skill in the art would have been motivated to do so in order to prepare libraries by split and recombine methodology and additionally to be able to encode the

chemical synthesis. One of ordinary skill in the art would reasonably have expected to be successfull because split and recombine techniques and encoding techniques were established practices in the art at the time of the invention

Applicant's arguments filed 10/6/99 have been fully considered but they are not persuasive.

Applicants argue that the Pavia et al teach compounds wherein both rings are aromatic or unsaturated and that Pavia excludes purines. Applicants assert that the claimed invention is directed to mixtures where the pyrimidines are substituted with saturated heterocycles and that unsaturated or aromatic heterocycles are not included in the invention.

This argument has been considered but is not found persuasive because as amended claim 32 recites for structure 1 that L can be "a mixed heterocycle or a substituted mixed heterocycle" (see page 3 of the 10/6/99 amendment in the third and forth line from the bottom of the page). As such, the heterocycles of Pavia et al read on the instant claims.

Therefore, the rejection is maintained for the reasons above and for the reasons of record.

Claim Rejections - 35 USC § 103

32. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

33. Claims 2-5, 7-15, 19, 26 and 32, rejected under 35 U.S.C. 103(a) as being unpatentable over Freeman et al [3,670,077] and Kraatz et al [US 4,978,382] and Drabek [US 4,215,122] and Moore [US 4,016,275] in view of Henrie [US 5,587,379 or 5,521,192] and further in view of In re Kerkhoven, 626 F.2d 846, 850, 205.

USPQ 1069, 1072 (CCPA 1980)

Freeman et al teach pyrimidine insecticides and composition thereof, which read on structure I when: R5 is H, R2 R4 and R6 are an organic radical, both N atoms attached to the ring can be tethers substituted by R1 and R7 which are hydrogen atoms (equivalent to the claimed tether R3 being NR6 where R6 is H and the other groups are not present).

Kraatz et al teach pesticides based upon on 2-alkylthio pryimidines and composition thereof which read on structure I of the instant claims. The compound of Kraatz et al read on the instant claims at least when: the S at C2 is a tether as in applicants invention, R1 is halogen alkyl (which reads on the substituted alkyl) and R is a halogen or alkyl group. Example compounds are set forth in Table 1 (e.g., compounds 3, 6, 7, 9, 10, 17 etc.)

Drabek et al teach pyrimidine based insecticides and composition thereof, which read on structure I of the instant claims at least when: R4 is hydrogen; the nitrogen attached to C2 along with R2 is a tether (equivalent to applicants tether where R3 is NR6 and the other groups are not present), R3 is methyl or ethyl; the group at C6 containing R1 has n set to zero and R1 is alkyl or allyl (which reads on L being an ether having 1 sulfur atom and the tether being a bond); the

group at C4 is reads on a tether consisting of R5 being oxygen, R4 is keto and R3 is NR6 where R6 is methyl and the attached L group is methyl.

Moore teaches pyrimidine based insecticides, and composition thereof, which read on the instant claims at least when: the l attached to C2 is disulfide, R1 is hydrogen (R1 is preferably hydrogen, col. 1 line 54): and R and R2 are preferably hydrogen, halogen or C1-C4 alkyl.

As each of the above references teach pyrimidines the scaffolds have at least three functionalizable atoms, at least one of which is nucleophilic (the four carbons of the pyrimidine) the references read on claims 5 and 7. As the tethers contain functionalizable atom (or L groups could not be attached) which may be nucleophilic the references read on claim 8 and 9. As the tether have other atoms and groups attached, which reads on chemical substituents, the references read on claim 10, and as the substituents can have electrophilic groups the references read on claim 11 and 12. As each of the compounds set forth is a substituted pyrimidine, the position on which the substituents such as alkyl are attached are chemically blocked as required by claim 13. As the reference teach the compounds are insecticides, the references read on claim 26.

The references as combined above do not explicitly teach making mixtures of at least six pyrimidine containing compounds as insecticides.

Both of the Henrie et al references teach that preparation of pyrimidine insecticide formulated to contain a mixture of pyrimidines are known in the art. See column 63 lines 39-41 of the '192 patent and column 62 lines 59-61 of the '379 patent.

In *In re Kerkhoven* it is set forth that: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . . [T]he idea of combining them flows logically from their having been individually taught in the prior art."

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to prepare mixtures of pyrimidine based insecticides as taught by the Henrie references using the pyrimidine based insecticides as taught by Freeman, Kraatz, Drabek and Moore references because it is obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. Moreover, the art recognized that making mixtures of pyrimidine based insecticides for use as insecticides was known in the art. One of ordinary skill in the art would have been motivated to do so in order to form an active insecticide. One of ordinary skill in the art would have reasonably expected to be successful because each of the individual composition were known to have insecticidal activity and the combined compositions would have also been expected to be an effective pesticide.

34. Claims 32, 2-10, 13-15 and 17 are rejected under 35 U.S.C. 103(a) as being obvious over Summerton et al [5,506,337].

Summerton et al teach the formation of morpholino subunit libraries. These libraries having substituted purine heterocycles present (see figs 5a and 5b note that adenine is set forth in Figure 5a, top left structure, and struture 3 in figure 5b read on the claimed purines) which read on the purine heterocyclic scaffold of the instant invention. Summerton et al. teach that the

purine can be substituted a morpholino subunit which attaches the purine nucleotides to other bases reads on a tether with at least one functionalizable atom substituted with a chemical substituent (a limitation of claims 8 and 10). Alternatively, the morphilino group can be view as a substituent on a purine scaffold. The other morphilino bases in the oligomers of Summerton et al read on different chemical substituents. Any mixture of these which employs adenine as a base, as set forth above with more than six different sequences attached as substituents reads on the mixtures of the instant application. Summerton et al teach the libraries preferably contain 10^4 to 10^7 different sequences, which reads on the limitation of claims 2, 3, 21 and 22 (col 11 lines 43-56). Summerton et al teach that roughly equimolar mixtures of oligomers can be made by adjusting the concentration of each subunit which reads on the limitation of claim 4 (compounds are within 20 mole percent of equimolarity in the mixture). As a purine (adenine) has at least three functionalizable atoms the reference reads on claim 5. When the morphiline is considered a tether then the reference reads on claim 6 and 10. The purine scaffolds contain nitrogen atoms which read on nucleophilic atoms in the scaffolds, a specific limitation of claims 7. The morphilino group contains a nitrogen which reads on a functionalizable group of the tether being nucleophilic, a specific limitation of claim 9. Summerton et al teach that esters can be a substituent on the morphilino groups (figure 5C compound number 5 where X is OR) this reads on an electrophile since the group present would be subject to nucleophilic attack (Michael addition). As the morphilino group function to chemically block a funtionalizable atom of the scaffold, the specific limitation of claim 13. Summerton et al teach that the use of iterative synthesis to create the molecules of the mixtures, a limitation of claim 15 (synthesis requiring

repeated cycles of applying groups, removing protecting groups etc., see figure 13), and subsequent reactions as required in claim 17. Summerton et al teach that the compounds of their invention can be synthesized on solid supports or in solution, a limitation of claim 14 (Col 12 lines 3-8 and col 17 starting line 25).

The reference does not explicitly recite requiring the mixtures to have a purine nucleobase such, as adenine, reading on the claimed structure.

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to prepare a mixture comprising at least six morpholino compounds having adenine as a nucleobase when preparing a combinatorial library by the method of Summerton et al because Summerton et al teach that the libraries of molecules of the instant invention can hybridize with DNA and act as probes for random sequence oligonucleotides, (see claim 5). One of ordinary skill in the art would have been motivated to incorporate adenine into the morphilino combinatorial library to provide a base to pair with thymine containing nucleotides in the random DNA sequences to be hybridize. One of ordinary skill in the art would have reasonably expected to be successful because the Summerton et al had already achieved the preparation of morphilino based combinatorial libraries.

35. Claims 32, 2-10, 13, 17 and 24-26 are rejected under 35 U.S.C. 103(a) as being obvious over Neilsen et al [5,539,082].

Neilsen et al teach the formation peptide nucleic acids (PNA) and state

"Particularly preferred are compounds having formula (IIIa) or (IIIb) wherein each L is independently selected from the group consisting of the nucleobases thymine (T), adenine (A), cytosine (C), guanine (G) and uracil (U), k and m are zero or 1, and n is an integer from 1 to 30, in particular from 4 to 20.

These libraries have purine (A and G) heterocycles present which reads on structures II and III of the instant claims. Note that the remaining portion of the PNA molecules can at least be considered an L group which is capable of hydrogen bonding. Alternatively, the amino acid side chain joining the base to the backbone can be considered to be a tether read on the tethers of the instant claims (see column 3 and figure IIIa for example) and the remainder of the molecule is considered to be an L capable of at least hydrogen bonding. The reference teaches forming the multiple PNA molecules using method applicable to the formation of large numbers of peptides, including the method of Houghten (teabag method), which reads on forming a mixture and renders obvious mixtures with more than 15 compounds as required by claims 2 and 3, see column 20, lines 40-63 for example. As the Houghten teabag method is employed wherein the amount of each compound prepared is proportional to the number of sights on the beads which are quite uniform, the reference renders obvious the limitation of claim 4. As purines have at least three functionalizable atoms, the reference reads on claim 5. When the amino acid side chain is considered a tether then the reference reads on claim 6 and 10. In that purine scaffolds contain nitrogen atoms, which read on nucleophilic atoms in the scaffolds, the reference reads on claim 7. As the tether group may contain a nitrogen, which reads on a nucleophilic functionalizable group, (see figure IIIa spanning col. 2 and 3), the reference reads on claim 8 and 9. As the remainder the PNA chain attached to a nucleobase through an amino acid side chain tether (as set forht

above) reads on an L group and different sequences may be prepared in a set of PNA molecules the reference renders obvious the use of a set of substituents attached to a tether as required by claim 10. As the side chain tether functions to chemically block a funtionalizable atom of the purine scaffolds, the specific limitation of claim 13 is met. As the reference uses iterative synthesis adding on each subunit of the PNA molecules in succession, the reference reads on claim 17. The reference explicitly teaches with respect to PNA molecules that:

> "These are foreseen as extremely useful drugs for treating diseases like cancer, AIDS and other virus infections, and may also prove effective for treatment of some genetic diseases." and that "r PNA molecules are particularly relevant for purposes such as screening for antiviral effects"

which reads on viral disease as set forth by claim 25. In addition, the reference teaches that it is an object of the invention to provide a means for killing viruses or cells by contacting them with PNA molecules (see col. 7, lines 1-9), which renders obvious claims 24-26

The reference does not explicitly recite requiring the mixtures to have a purine nucleobase such, as adenine, reading on the claimed structure.

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to prepare a mixture comprising at least six PNA compounds having A or G as a nucleobase when preparing a multiple PNA molecules as taught by Neilsen et al because the reference teaches the PNA molecules act by hybridizing with DNA. One of ordinary skill in the art would have been motivated to incorporate A or G into the PNA molecules library to provide a base to pair with T and C residues of target nucleic acids. One of ordinary skill in the art would have reasonably expected to be successful because Neilsen et al had already achieved the preparation of PNA molecules incorporating A and G bases.

36. The species of six compounds elected by applicants is free of the prior art of record.

37. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph W. Ricigliano Ph. D. whose telephone number is (703) 308-9346. The examiner can be reached on Monday through Thursday from 7:00 A.M. to 5:30 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Keith MacMillan, can be reached at (703) 308-4614.

Joseph W. Ricigliano Ph.D. 4/7/00

Joseph W. Ricigliano Ph. D.

April 7, 2000